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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,169	11/28/2005	Roger R. C. New	117-565	7760

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

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09/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,169	NEW, ROGER R. C.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-15,18-24 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-15,18-24 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-7, 9-15, 18-24 and 26-30 are pending.

Claim Objections

2. The objection to claims 5, 12 and 23 is withdrawn in light of the amendment to the claim filed 06/01/2007.

Claim Rejections - 35 USC § 112

3. The rejections of claims 1-10, 12-15, 18-20, and 22-26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirements, are withdrawn in light of the amendments and arguments filed 06/01/2007.

4. The rejection of claim 23 under 35 U.S.C. 112, second paragraph, is withdrawn in light of the amendment to the claim filed 06/01/2007.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Applicant has not submitted arguments with respect to the rejection of claims 1-15 and 18-26 but has amended claim 1.

7. Claims 1-7, 9-15, 18-24 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over New (U.S. Patent No. 5,853,748) in view of Makino *et al.* (JP 56138168A), Modi *et al.* (U.S. Patent No. 5,653,987) and Desai (U.S. Patent No. 5,206,219).

8. New teaches a pharmaceutical composition of a macromolecular principle (insulin), a bile acid (chenodeoxycholic acid) and an additive that buffers the gut to pH 7.5-9 (sodium bicarbonate, example 4). Regarding the newly added limitation in claims 1, 26 and new claims 27-30, the composition is coated with an enteric coating designed to prevent digestion in the stomach and to permit digestion in the small intestine (column 7, lines 37-40). The pH of the small intestine is neutral and falls within the claimed range, as evidenced by Alberts *et al.* Molecular Biology of the Cell, 4th ed., chapter 22.

9. Regarding claims 26 and 24, New also teaches a method of enhancing the absorption of the insulin across the intestinal well in an animal body comprising administering the insulin/chenodeoxycholic acid/sodium bicarbonate composition. Regarding claims 2 and 22, the composition comprises less than 5% by weight of water (table in example 4). Regarding claim 4, the additive, sodium bicarbonate, is present at 8.3% by weight which is great than 1% (table in example 4). Regarding claim 5, the ratio by weight of the chenodeoxycholic acid plus the additive to the insulin is 10:1 which is greater than 5:1 (table in example 4). Regarding claims 6 and 7 and 23, the composition is in the form of a solution (column 7, lines 50-55) or a solid (example 4). Regarding claims 8-11 and 18-21, the active macromolecular principle is insulin. Regarding claims 11 and 21, the composition sensitizes the subject to insulin by increasing uptake (example 4). Regarding claim 12, the non-conjugated bile acid is chenodeoxycholic acid, the acidic form of chenodeoxycholate. Regarding claim 15, the composition is for therapeutic use in a human or animal (example 4).

10. New does not teach that the additive can be propyl gallate.

11. Makino *et al.* teach a pharmaceutical composition comprising an active ingredient and a bile acid, such as deoxycholic, cholic or apocholic acid, and an antioxidant such butylhydroxytoluene, propyl gallate or lecithin each present at 10-100,000 and 10-10,000 times that of the active ingredient, respectively (abstract).

12. Desai teaches that antioxidants like butylated hydroxyanisole, butylated hydroxytoluene, d-α-tocopherol, and propyl gallate are commonly used in pharmaceutical compositions of insulin and other protein active ingredients (column 5, lines 5-18).

13. It would have been obvious to one of ordinary skill in the art to substitute the propyl gallate for the sodium bicarbonate in the pharmaceutical composition taught by New and to use it treat diabetes (claim 25). The skilled artisan would have been motivated to do so given that the pKa of propyl gallate is 8.11 (CRC Handbook of Chemistry and Physics) and that New teaches that additives that buffer the gut between pH 7.5 and 9 increase the bioavailability of the insulin while limiting the toxicity of the bile acids (column 5, lines 10-18). The skilled artisan would have been further motivated by Makino *et al.* who teach that the bile acid and antioxidant combination renders the pharmaceutical stable to light and heat for a long period of time (abstract), Desai who teaches that antioxidants are commonly used, and Modi *et al.* who teach that it is usual to add at least one antioxidant to prevent degradation and oxidation of pharmaceutically active ingredients (column 3, lines 33-36). There would have been a reasonable expectation of success given that that propyl gallate is commonly used in pharmaceutical compositions and has an appropriate pKa for buffering a solution between pH 7.5 and 9, and that New demonstrated that insulin and bile acids are compatible. Thus, the invention

as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

14. Regarding claim 14, it would have been obvious to one of ordinary skill in the art to substitute butyl hydroxyl anisole for the sodium bicarbonate in the pharmaceutical composition taught by New and to use it treat diabetes (claim 25). The skilled artisan would have been motivated to do so given that the pKa of butyl hydroxyl anisole is 7.5 (Ivanovic *et al.*, *Chromatographia*, **1995**, *40*, 652-6) and that New teaches that additives that buffer the gut between pH 7.5 and 9 increase the bioavailability of the insulin while limiting the toxicity of the bile acids (column 5, lines 10-18). The skilled artisan would have been further motivated by Makino *et al.* who teach that the bile acid and antioxidant combination renders the pharmaceutical stable to light and heat for a long period of time (abstract), Desai who teaches that antioxidants are commonly used, and Modi *et al.* who teach that it is usual to add at least one antioxidant to prevent degradation and oxidation of pharmaceutically active ingredients (column 3, lines 33-36). There would have been a reasonable expectation of success given that that propyl gallate is commonly used in pharmaceutical compositions and has an appropriate pKa for buffering a solution between pH 7.5 and 9, and that New demonstrated that insulin and bile acids are compatible. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

15. Regarding claims 11 and 21, it would have been further obvious to use a known insulin sensitizing agent in the pharmaceutical composition. Sonnenberg & Kotchen (*Curr. Op. Neph. Hyperten.*, **1998**, *7*, 551-5) teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. The skilled artisan would have been motivated to use it in the

composition taught by New because Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involing diabetic patients (page 552). There would have been a reasonable expectation of success because the U.S. Food and Drug Adminitsrtaion has approved the use of troglitazone in combination with insulin (page 552). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

16. The rejection of claims 1-15 and 18-26 on the ground of nonstatutory obviousness-type double patenting over claims 30-58 of copending Application No. 10/553,324 is withdrawn in light of the terminal disclaimer filed 09/07/2007.

Conclusion

17. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

19. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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